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Reduced-Intensity Transplantation for Patients with Myelodysplastic Syndrome Achieves Durable Remission with Less Graft-versus-Host Disease

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ABSTRACT

Reduced-intensity allogeneic transplantations for myelodysplastic syndrome (MDS) patients have been limited by significant graft-versus-host disease (GVHD), treatment-related mortality, and disease relapse. We treated 18 MDS patients ineligible for standard allogeneic transplantation with a preparative regimen of photopheresis day −7 and −6, pentostatin 4 mg/m^2 by continuous infusion day −5 and −4, and total body irradiation 600 cGy in 3 fractions day −3 and −2, followed by allogeneic stem cell infusion from 6/6 or 5/6 HLA-matched related donors or 6/6 HLA-matched unrelated donors. GVHD prophylaxis consisted of cyclosporin A and a short course of methotrexate. The median age was 54 years (range, 30-70 years). Diagnoses included refractory anemia (n = 2), refractory anemia with ringed sideroblasts (n = 2), refractory anemia with excess blasts (n = 10), refractory anemia with excess blasts in transformation (n = 3), and chronic myelomonocytic leukemia (n = 1). Sixteen of 18 patients developed full donor chimerism with no day +100 transplant-related mortality. Grade II to IV acute GVHD and extensive chronic GVHD developed in 19% and 18% of patients, respectively. Disease relapse occurred in 2 patients. At a median follow-up of 14 months (range, 1-35 months), the 1-year failure-free and overall survival were 64% and 65%, respectively. Our photopheresis and pentostatin–based reduced-intensity preparative regimen for allogeneic bone marrow transplantation in high-risk MDS patients achieves successful donor engraftment and disease remission with less transplant toxicity and grade II to IV acute GVHD.

KEY WORDS

Reduced-intensity conditioning • MDS • Photopheresis • Pentostatin

INTRODUCTION

The myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders characterized by ineffective hematopoiesis; they manifest clinically as anemia, neutropenia, and thrombocytopenia [1]. Patients with the French-American-British (FAB) classification of refractory anemia with excess blasts (RAEB) or refractory anemia with excess blasts in transformation have a median survival of <12 months [2]. Allogeneic stem cell transplantation offers the only curative treatment, with an estimated 3-year disease-free survival probability of 25% in patients with matched unrelated donors and 28% in patients with matched related donors [3]. However, ablative doses of chemotherapy and radiation are associated with high incidences of treatment-related mortality (TRM) and graft-versus-host disease (GVHD), preventing most MDS patients from receiving conventional transplantation. Reduced-intensity preparative regimens have enabled successful donor engraftment in MDS patients ineligible for conventional transplantation because of advanced age, poor performance status, or comorbidities. However, MDS patients undergoing reduced-intensity transplantation experience high incidences of TRM (33%-48%), GVHD (33%-

Table 1. *Patient Characteristics*

Patient No.	Age (y)/Sex	Type/FAB	IPSS Group	BMT Type	Sex Mismatch	Host/Donor CMV Status	Prior BMT	Prior Chemotherapy
1	59/M	Primary/RAEB	High	5/6 Allo	Yes	−/−	No	Induction, recover, then BMT
2	58/M	Primary/RAEB	Int-1	5/6 Allo	Yes	−/−	No	Induction into BMT
3	70/M	Primary/RAEB	Int-1	6/6 Allo	Yes	−/+	No	No
4	61/F	Secondary/RAEB	Int-2	5/6 Allo	No	+/+	Auto	No
5	45/F	Primary/RAEB	Int-2	6/6 Allo	No	+/+	No	Induction, recover, then BMT
6	59/M	Primary/RAEB	Int-1	6/6 Allo	No	−/+	No	No
7	32/F	Secondary/RAEB	Int-1	6/6 Allo	Yes	−/−	No	Induction into BMT
8	35/F	Secondary/RAEBT	Int-1	6/6 Allo	Yes	+/−	Auto	No
9	41/F	Primary/RA	Low	6/6 Stem	No	+/−	No	No
10	53/F	Primary/CMML	Int-1	6/6 Allo	Yes	+/+	No	Induction into BMT
11	60/F	Primary/RARS	Int-1	6/6 MUD	Yes	−/−	No	Induction, recover, then BMT
12	47/F	Primary/RAEB	Int-2	6/6 MUD	No	−/+	No	Induction into BMT
13	61/M	Primary/RAEB	High	5/6 Allo	No	+/−	No	No
14	56/F	Primary/RAEBT	High	6/6 Allo	No	+/+	No	Induction, recover, then BMT
15	42/F	Secondary/RAEBT	Int-2	6/6 MUD	Yes	+/−	No	Induction, recover, then BMT
16	51/M	Primary/RAEB	Int-2	6/6 MUD	Yes	+/−	No	No
17	60/F	Secondary/RARS	Int-1	6/6 Allo	No	−/+	No	No
18	30/M	Primary/RA	Int-1	6/6 Allo	No	+/+	No	No

Allo indicates allogeneic bone marrow stem cells; Stem, peripheral blood stem cells; MUD, matched unrelated donor bone marrow stem cells; Auto, autologous stem cell transplantation; BMT, bone marrow transplantation; Int, intermediate; RAEBT, refractory anemia with excess blasts in transformation; RA, refractory anemia; RARS, refractory anemia with ringed sideroblasts.

43%), and disease relapse (33%-42%), resulting in poor overall survival (26%-39%) [4-6]. We report the results of a novel reduced-intensity preparative regimen for allogeneic stem cell transplantation in high-risk MDS patients that combines durable donor engraftment and disease remission with minimal TRM and GVHD.

MATERIALS AND METHODS

Patient Characteristics

Between January 2000 and February 2003, 18 high-risk MDS patients underwent reduced-intensity allogeneic stem cell transplantation at Tufts–New England Medical Center (Table 1). The median recipient age was 54 years (range, 30-70 years). There were 7 men and 11 women. Thirteen patients had primary MDS, whereas 5 patients developed MDS as a complication of prior therapy for Hodgkin disease (n = 2), non-Hodgkin lymphoma (n = 1), breast cancer (n = 1), or multiple myeloma (n = 1). Diagnoses by FAB classification included refractory anemia (n = 2), refractory anemia with ringed sideroblasts (n = 2), RAEB (n = 10), refractory anemia with excess blasts in transformation (n = 3), and chronic myelomonocytic leukemia (n = 1). Classification by the International Prognostic Scoring System (IPSS) [7] included low (n = 1), intermediate-1 (n = 9), intermediate-2 (n = 5), and high (n = 3). Risk factors for GVHD included 5 of 6 HLA-matched related donors (n = 4), 6 of 6 HLA-matched unrelated donors (n = 4), granulocyte colony-stimulating factor–stimulated peripheral blood stem cells (n = 1), female donor to male recipient (n = 4), and cytomegalovirus (CMV)–seropositive recipient (n = 10). Two patients underwent prior autologous stem cell transplantation for multiple myeloma (n = 1) or Hodgkin disease (n = 1). Four patients underwent induction chemotherapy followed immediately by the preparative regimen, whereas 5 patients underwent induction chemotherapy followed by marrow recovery before the preparative regimen was initiated. Patients were ineligible for conventional allogeneic stem cell transplantation because of 1 or more of the following risk factors: age >50 years (n = 11), secondary MDS (n = 5), poor performance status from prior chemotherapy (n = 2), morbid obesity (n = 1), or recurrent bleeding complications (n = 3).

Transplant Preparative Regimen, GVHD Prophylaxis, and Supportive Care

Patients received extracorporeal photopheresis (ECP) day −7 and −6, pentostatin 4 mg/m^2 by continuous infusion day −5 and −4, and total body irradiation 600 cGy in three 200-cGy fractions day −3 and −2. On day 0, unmanipulated allogeneic stem cells from bone marrow (n = 17) or granulocyte colony-stimulating factor–stimulated peripheral blood (n = 1) were infused.

GVHD prophylaxis consisted of cyclosporin A 2.5 mg/kg/d by continuous infusion starting on day −1 and converting to oral cyclosporin A when tolerated, tapering off after day +100 [8]. Methotrexate 15 mg/m^2 was given on day +1 and 10 mg/m^2 on day +3. Mycophenolate mofetil 1000 mg orally twice per day was started on day +100 and tapered off after day +365 in the absence of GVHD. Methylprednisolone

Table 2. *Patient Results*

Patient No.	Days to ANC $>5 \times 10^9$/L	Days to PLT $>20 \times 10^9$/L	Chimerism at Engraftment	Acute GVHD	Chronic GVHD	Disease Status	Overall Status	Outcome
1	14	32	99% donor	I	None	CR	Alive	No chronic GVHD
2	16	54	100% donor	II	Extensive	CR	Died	Skin chronic GVHD. Died of cerebrovascular event
3	9	25	99% donor	I	Limited	CR	Alive	Oral chronic GVHD
4	16	35	Host	NA	NA	PD	Died	Died of progressive disease
5	12	18	Donor	I	None	CR	Alive	No chronic GVHD
6	15	22	Donor	I	Limited	CR	Alive	Oral chronic GVHD
7	24	18	61% donor	I	Limited	CR	Died	100% donor by day +91. Skin chronic GVHD, died of idiopathic pulmonary syndrome
8	17	18	95% donor	0	Limited	CR	Alive	No chronic GVHD
9	24	51	Mixed	0	Limited	CR	Alive	100% donor at day +100. Skin chronic GVHD
10	16	16	90% donor	0	Extensive	CR	Alive	Skin chronic GVHD
11	11	17	99% donor	III	Extensive	CR	Died	Died of gut chronic GVHD
12	15	99	Donor	IV	Extensive	CR	Died	Died of gut chronic GVHD
13	40	59	Host	NA	NA	PD	Died	Died of progressive disease
14	15	8	Donor	I	None	Relapse	Died	Died of progressive disease
15	12	16	Donor	I	None	CR	Alive	No chronic GVHD
16	15	24	Donor	0	None	CR	Alive	No chronic GVHD
17	25	39	Donor	0	NA	Relapse	Died	Died of progressive disease
18	24	27	Donor	I	None	CR	Alive	No chronic GVHD

ANC indicates absolute neutrophil count; PLT, platelet count; CR, complete response; PD, progressive disease; NA, not applicable.

1 mg/kg was used for treatment of GVHD and tapered off when GVHD symptoms resolved.

Antimicrobial prophylaxes were performed according to institutional protocols. These included trimethoprim/sulfamethoxazole for *Pneumocystis carinii* prophylaxis and acyclovir for herpes simplex virus prophylaxis.

Outcomes

Complete response was defined as normal trilineage hematopoiesis with the absence of MDS by bone marrow biopsy and the absence of circulating blasts. Progressive disease was defined as the persistence of MDS morphology by bone marrow biopsy after transplantation or the persistence of circulating blasts. Disease relapse was defined as the presence of MDS morphology by bone marrow biopsy or the presence of circulating blasts after a complete response was achieved. Chimerism was determined at the time of neutrophil engraftment by fluorescent in situ hybridization for the Y chromosome in cases of sex-mismatched transplants or by polymerase chain reaction of polymorphic short tandem repeats in cases of sex-matched transplants. Clinical response was defined according to the international working group on standardizing response criteria in MDS [9]. Standard criteria were used to diagnose and grade acute and chronic GVHD [10]. Regimen-related toxicity was graded by using the system of Bearman et al. [11].

Statistics

Transplant-related mortality was defined as any cause of death in the absence of disease progression or relapse. Failure-free survival was defined as time to disease progression or death from any cause. Failure-free survival and overall survival were estimated with the Kaplan-Meier method. Chi-square tests were used to examine the association between various patient characteristics and transplant outcomes. A P value of $<.05$ was considered statistically significant.

RESULTS

Engraftment and Chimerism

Sixteen (89%) of 18 patients developed full donor chimerism (>90% donor), and 14 patients achieved full donor chimerism at the time of engraftment (Table 2). Two patients reached full donor chimerism by day +100 without donor lymphocyte infusion. Two patients did not engraft and had full autologous hematopoietic reconstitution. The median time to reach an absolute neutrophil count $>5 \times 10^8$/L for 3 consecutive days was 15 days (range, 9-40 days). The median time to reach a platelet count of 20×10^9/L with transfusion independence was 20 days (range, 8-59 days).

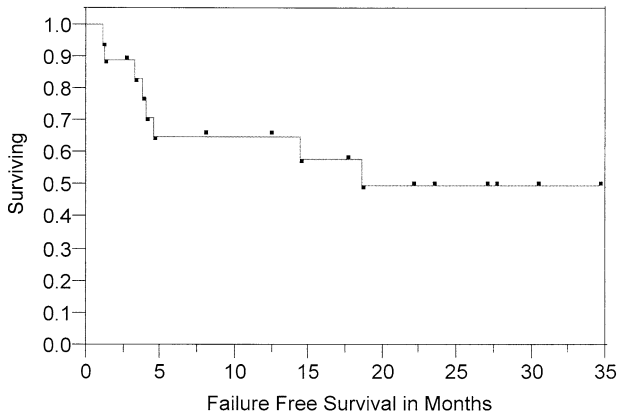

Figure 1. Failure-free survival in patients with MDS after the photopheresis and pentostatin reduced-intensity preparative regimen.

Graft-versus-Host Disease

Thirteen patients (81%) had grade 0 (n = 5) or I (n = 8) acute GVHD. One patient developed grade III acute GVHD of the skin, and 2 patients developed grade III or IV acute GVHD of the gut, for an overall 19% incidence of grade II to IV acute GVHD. No one died from acute GVHD before day +100. Eight patients (53%) had no evidence of chronic GVHD. Limited chronic GVHD developed in 4 patients (27%), and extensive chronic GVHD of the skin developed in 3 patients (20%).

Transplant Toxicity

According to the Bearman score, no patients experienced grade 3 or 4 mucositis, liver, or renal toxicity. Grade 1 or 2 mucositis was seen in 9 and 2 patients, respectively. Ten patients had grade 1 liver toxicity, and 1 patient had grade 2 liver toxicity. Grade 2 renal toxicity was seen in 1 patient, and grade 1 renal toxicity was seen in 10 patients. No patient experienced veno-occlusive disease. CMV reactivation was seen in only 3 patients (17%), and all were successfully treated with valganciclovir therapy. No one died of transplant-related complications before day +100. The 1-year TRM was 14%. There were 8 deaths in this study. Three patients died from complications related to extensive chronic GVHD while in complete remission. One patient in complete remission died of idiopathic pulmonary syndrome 19 months after transplantation. Both patients whose donor engraftment failed died of disease progression. Two patients who had donor engraftment died of disease relapse.

Response and Survival

Out of 16 patients who demonstrated durable donor engraftment, 14 patients (88%) achieved clinical complete remission with the absence of circulating or bone marrow blasts and normal trilineage hematopoiesis. Two patients (13%) developed disease relapse 39 and 117 days after donor engraftment. Both patients died of disease progression before donor lymphocyte infusion could be given. After a median follow-up of 14 months (range, 1-35 months), the 1-year failure-free survival was 64% (Figure 1). The 1-year overall survival was 65% (Figure 2). Ten patients were alive and free from clinical disease at the time of analysis.

Prognostic Factors

GVHD severity and overall survival were not markedly different by FAB subtypes, IPSS scores, or patient age (Table 3). However, MDS patients who received transplants from 6 of 6 HLA-matched related donors had a lower incidence of grade II to IV acute GVHD as compared with mismatched related and matched unrelated donors (0% versus 50%; $P = .01$) and had better 1-year overall survival (71% versus 57%; $P = .19$; Figure 3). The incidence of disease relapse did not differ in the setting of grade II to IV acute GVHD (15% versus 0%; $P = .47$) or limited or extensive chronic GVHD (14% versus 0%; $P = .27$).

DISCUSSION

Conventional allogeneic stem cell transplantation, although curative for MDS patients, is associated with successful donor engraftment (91%) and a low incidence of disease relapse (17%) but with high incidences of TRM (37%), grade II to IV acute GVHD (36%), and chronic GVHD (39%), resulting in a 3-year disease-free and overall survival of only 23% and 40%, respectively [12]. Reduced-intensity preparative regimens rely on host immunosuppression instead of ablative doses of chemoradiation to minimize TRM while facilitating donor stem cell engraftment to achieve disease remission through a graft-versus-tumor effect. However, fludarabine-based reduced-intensity preparative regimens for allogeneic trans-

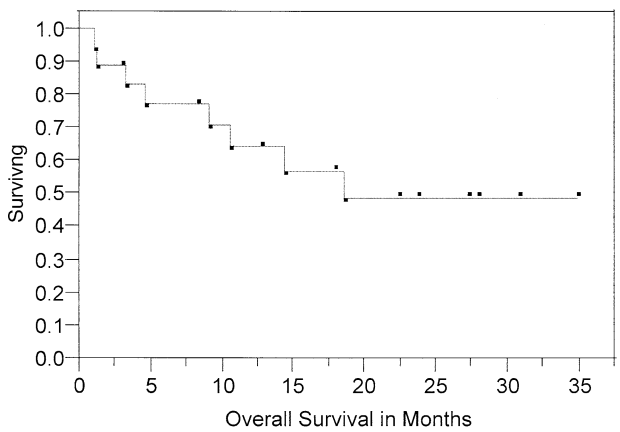

Figure 2. Overall survival in patients with MDS after the photopheresis and pentostatin reduced-intensity preparative regimen.

Table 3. *Prognostic Factors**

Factor	Grade II-IV Acute GVHD	1-Year Overall Survival
FAB subtypes		
RAEB or RAEBT	18%	68%
Others	20%	53%
P value	.93	.61
IPSS groups		
Low or intermediate-1	17%	79%
Intermediate-2 or high	20%	45%
P value	.87	.42
Age		
<50 y	14%	83%
≥50 y	22%	52%
P value	.69	.26
Induction chemotherapy		
Yes	33%	67%
No	0%	62%
P value	.09	.96
Donor match		
6/6 matched related donors	0%	71%
Mismatched related donors or matched unrelated donors	50%	57%
P value	.01	.19

RAEBT indicates refractory anemia with excess blasts in transformation.

*The incidence of grade II-IV acute GVHD and 1-y overall survival did not differ significantly when subdivided by FAB classification, IPSS groups, age, or prior induction chemotherapy. Donor match significantly increased the incidence of grade II-IV acute GVHD but did not affect 1-y overall survival.

plantation of MDS patients were complicated by high incidences of TRM (27%-48%), grade II to IV acute GVHD (33%-75%), chronic GVHD (38%-48%), and disease relapse (25%-33%), resulting in poor disease-free survival (12%-38%) and overall survival (26%-39%) [4-6,13].

In contrast, MDS patients who underwent a photopheresis and pentostatin–based conditioning regimen achieved early full donor chimerism with no 100-day TRM, 19% grade II to IV acute GVHD, and a 13% disease relapse rate, resulting in a 65% overall survival. Prompt establishment of full donor chimerism seems important in harnessing a maximum graft-versus-leukemia effect [14], and this was achieved with low transplant-related toxicity and no TRM. Our failure-free and overall survival were markedly higher than in a similar cohort of patients reported by Kroger et al. [6]. Although our study examined a small number of patients at a single institution, patient characteristics are unlikely to explain the different outcomes because the numbers of patients with older age, RAEB classification, and aberrant cytogenetics were similar in both studies.

The 19% incidence of severe grade II to IV acute GVHD was also markedly lower than the 33% to 75% reported in other reduced-intensity preparative regimens for MDS patients [5,6,13-16]. Although more patients received stem cells from matched unrelated donors in the study from Kroger et al., the patients we treated were at higher risk for GVHD because of advanced age, single antigen–mismatched related donors, and CMV recipient seropositivity, making the risk of GVHD similar in both groups. Stem cell source was unlikely to be the cause for the differences in GVHD because both studies used bone marrow stem cells. Successful donor engraftment in most patients and the low incidence of CMV reactivation suggest that the low incidence of GVHD was not achieved with excessive immunosuppression alone. Therefore, the reason why our regimen has a markedly lower incidence of severe acute GVHD may be related to our novel preparative regimen.

The pathophysiology of acute GVHD is complex and involves the release of host antigens after damage to host tissues with the preparative regimen; it also involves the presentation of host antigens by host dendritic cells (DCs) to donor T cells in the context of major histocompatibility complex molecules to activate $CD8^+$ cells, thereby initiating the proinflammatory cytokine cascade [17]. In murine studies, inactivation of host DCs before transplantation abrogated GVHD, suggesting that host DCs that linger after transplantation may play an important role in the pathogenesis of acute GVHD [18]. In human transplants, alemtuzumab given before transplantation has been shown to deplete circulating host DCs, resulting in the absence of host DCs and a low incidence of acute posttransplantation GVHD [19]. However, the low rate of acute GVHD may also be related to the effects of in vivo T-cell depletion by the prolonged half-life of alemtuzumab, resulting in increased inci-

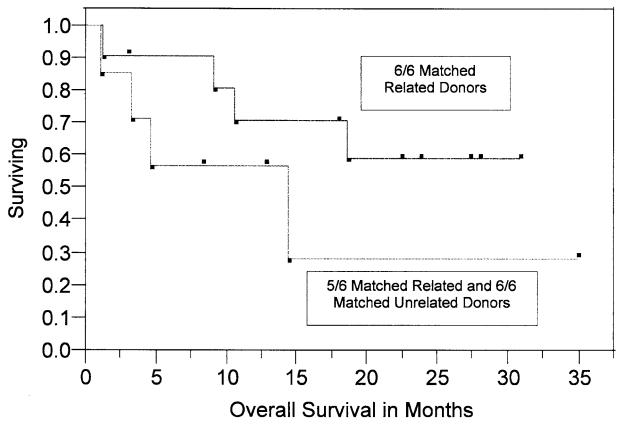

Figure 3. Overall survival by donor match in patients with MDS after the photopheresis and pentostatin reduced-intensity preparative regimen. The top curve represents 6 of 6 matched related donors. The bottom curve includes 5 of 6 matched related donors and 6 of 6 matched unrelated donors (1-year overall survival, 71% versus 57%; $P = .19$)

dences of engraftment failure, CMV reactivation, and disease relapse [20].

ECP involves the ex vivo exposure of leukapheresed peripheral blood mononuclear cells to ultraviolet A light in the presence of a DNA-intercalating agent, 8-methoxypsoralen, with subsequent reinfusion of treated cells. The total number of lymphocytes treated ex vivo per cycle has been estimated to be between 5% and 15% of the total circulating lymphocytes, and the total energy delivered via ultraviolet A light is estimated to be 2 J/cm^2 per lymphocyte [21]. ECP has been used successfully to treat acute and chronic GVHD that is refractory to conventional immunosuppression [22,23]. In the treatment of chronic GVHD, ECP decreases the number of DCs while shifting from DC1 subtypes that promote proinflammatory cytokine secretion to DC2 subtypes that are associated with immune tolerance [24]. DC chimerism studies in patients after our ECP and pentostatin–based preparative regimen demonstrated that the absence of severe acute and chronic GVHD was associated with the absence of host DCs after transplantation, whereas the persistence of host DCs after transplantation was associated with severe acute and extensive chronic GVHD [25]. Decreases in DC1 and DC2 numbers after ECP in the preparative regimen have been observed in patients who remain in complete remission in the absence of host DCs or GVHD after transplantation [26].

No significant differences in the incidence of grade II to IV acute GVHD or in overall survival were observed between FAB subtypes, IPSS groups, or age, suggesting that patients with advanced MDS tolerate this preparative regimen as well as patients with less advanced MDS. Remarkably, there was no difference in overall survival between patients who underwent transplantation directly and patients who required induction chemotherapy before transplantation for increasing blast counts, suggesting that induction chemotherapy before transplantation did not increase toxicity or mortality. As expected, transplants from mismatched related donors and matched unrelated donors resulted in a significantly higher incidence of grade II to IV acute GVHD, although the difference in overall survival was not significantly different. The absence of significant differences in overall survival between transplants with 6/6 matched related donors and HLA class I mismatched or matched unrelated donors suggests that the degree of donor match may not have an adverse effect on transplantation outcomes after this preparative regimen.

In contrast to a study by Martino et al. [13], disease remission in our study was not associated with development of acute or chronic GVHD. In fact, 8 of 10 patients with 6 of 6 matched related donors remained in complete remission without developing grade II to IV acute GVHD, suggesting that prevention of GVHD was not accomplished by compromising graft-versus-tumor effects. The low incidence of CMV reactivation also suggests that the low incidence of severe GVHD was not achieved through excessive impairment of immune function. The role that ECP and pentostatin play in reducing host DCs before transplantation and their effects on preventing the development of grade II to IV acute GVHD merit further investigation.

We acknowledge that the limited number of patients and early follow-up preclude any definitive conclusions. Further studies are needed to evaluate the role of ECP in modulating DCs and preventing the development of GVHD. However, we conclude that our photopheresis and pentostatin–based reduced-intensity preparative regimen enables patients with MDS to benefit from allogeneic stem cell transplantation with minimal GVHD, transplant-related toxicity, and mortality. The curative potential of this approach requires further exploration.

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REFERENCES

1. Heaney ML, Golde DW. Myelodysplasia. *N Engl J Med.* 1999; 340:1649-1660.
2. Bennett JM, Catovsky D, Daniel MT, et al. Proposals for the classification of the myelodysplastic syndromes. *Br J Haematol.* 1982;51:189-199.
3. de Witte T, Hermans J, Vossen J, et al. Haematopoietic stem cell transplantation for patients with myelo-dysplastic syndromes and secondary acute myeloid leukaemias: a report on behalf of the Chronic Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Br J Haematol.* 2000;110:620-630.
4. Rezvani K, Lalancette M, Szydlo R. Nonmyeloablative stem cell transplant in AML, ALL, and MDS: disappointing outcome for patients with advanced phase disease. *Blood*. 2000;96.
5. Kroger N, Schetelig J, Zabelina T, et al. A fludarabine-based dose-reduced conditioning regimen followed by allogeneic stem cell transplantation from related or unrelated donors in patients with myelodysplastic syndrome. *Bone Marrow Transplant.* 2001;28:643-647.
6. Kroger N, Bornhauser M, Ehninger G, et al. Allogeneic stem cell transplantation after a fludarabine/busulfan-based reduced-intensity conditioning in patients with myelodysplastic syndrome or secondary acute myeloid leukemia. *Ann Hematol.* 2003;82:336-342.
7. Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood.* 1997;89:2079-2088.
8. Miller KB, Schenkein DP, Comenzo R, et al. Adjusted-dose continuous-infusion cyclosporin A to prevent graft-versus-host

disease following allogeneic bone marrow transplantation. *Ann Hematol.* 1994;68:15-20.

9. Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood.* 2000;96:3671-3674.
10. Rowlings PA, Przepiorka D, Klein JP, et al. IBMTR Severity Index for grading acute graft-versus-host disease: retrospective comparison with Glucksberg grade. *Br J Haematol.* 1997;97: 855-864.
11. Bearman SI, Appelbaum FR, Buckner CD, et al. Regimen-related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol.* 1988;6:1562-1568.
12. Sierra J, Perez SW, Rozman C, et al. Bone marrow transplantation from HLA-identical siblings as treatment for myelodysplasia. *Blood.* 2002;100:1997-2004.
13. Martino R, Caballero MD, Simon JA, et al. Evidence for a graft-versus-leukemia effect after allogeneic peripheral blood stem cell transplantation with reduced-intensity conditioning in acute myelogenous leukemia and myelodysplastic syndromes. *Blood.* 2002;100:2243-2245.
14. Childs R, Clave E, Contentin N, et al. Engraftment kinetics after nonmyeloablative allogeneic peripheral blood stem cell transplantation: full donor T-cell chimerism precedes alloimmune responses. *Blood.* 1999;94:3234-3241.
15. Khouri IF, Keating M, Korbling M, et al. Transplant-lite: induction of graft-versus-malignancy using fludarabine-based nonablative chemotherapy and allogeneic blood progenitor-cell transplantation as treatment for lymphoid malignancies. *J Clin Oncol.* 1998;16:2817-2824.
16. Slavin S, Nagler A, Naparstek E, et al. Nonmyeloablative stem cell transplantation and cell therapy as an alternative to conventional bone marrow transplantation with lethal cytoreduction for the treatment of malignant and nonmalignant hematologic diseases. *Blood.* 1998;91:756-763.
17. Ferrara JL, Cooke KR, Pan L, Krenger W. The immunopathophysiology of acute graft-versus-host-disease. *Stem Cells.* 1996; 14:473-489.
18. Shlomchik WD, Couzens MS, Tang CB, et al. Prevention of graft versus host disease by inactivation of host antigen-presenting cells. *Science.* 1999;285:412-415.
19. Klangsinsirikul P, Carter GI, Byrne JL, Hale G, Russell NH. Campath-1G causes rapid depletion of circulating host dendritic cells (DCs) before allogeneic transplantation but does not delay donor DC reconstitution. *Blood.* 2002;99:2586-2591.
20. Cull GM, Haynes AP, Byrne JL, et al. Preliminary experience of allogeneic stem cell transplantation for lymphoproliferative disorders using BEAM-CAMPATH conditioning: an effective regimen with low procedure-related toxicity. *Br J Haematol.* 2000;108:754-760.
21. Knobler R. Extracorporeal photochemotherapy—present and future. *Vox Sang.* 2000;78:197-201.
22. Oliven A, Shechter Y. Extracorporeal photopheresis: a review. *Blood Rev.* 2001;15:103-108.
23. Greinix HT, Volc-Platzer B, Kalhs P, et al. Extracorporeal photochemotherapy in the treatment of severe steroid- refractory acute graft-versus-host disease: a pilot study. *Blood.* 2000; 96:2426-2431.
24. Alcindor T, Gorgun G, Miller KB, et al. Immunomodulatory effects of extracorporeal photochemotherapy in patients with extensive chronic graft-versus-host disease. *Blood.* 2001;98: 1622-1625.
25. Chan GW, Gorgun G, Miller KB, Foss FM. Persistence of host dendritic cells after transplantation is associated with graft-versus-host disease. *Biol Blood Marrow Transplant.* 2003;9:170-176.
26. Chan GW, Miller KB, Foss FM. Modulation of host dendritic cells by extracorporeal photopheresis in an allogeneic bone marrow transplant conditioning regimen. *Biol Blood Marrow Transplant*. 2003;9 abstr 105.